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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/299,562	04/27/99	HEGEDUS	[illegible]

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EXAMINER	
HAMILTON, L	

ART UNIT	PAPER NUMBER
1646	10

DATE MAILED: 03/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

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Office Action Summary

Application No.	Applicant(s)
09/299,562	Hegedus et al.
Examiner	**Group Art Unit**
Fozia Hamud	1646

☒ Responsive to communication(s) filed on *Dec 30, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-41* is/are pending in the application.

Of the above, claim(s) *24-29* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23 and 30-41* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-23, 30-41) in Paper No.9 filed on December, 30, 1999 is acknowledged.

The traversal is on the ground that Applicants preserve the right of filing a Divisional application directed to the non-elected invention at a later stage, and that upon an indication of allowable subject matter, Applicants request rejoinder of the process claims.

With respect to Applicants first ground of traversal, Applicants would be allowed to file a Divisional application directed to the non-elected invention at a later stage. With respect to the second ground of traversal, upon an indication of allowable subject matter, the process claims directed to the examined invention, will be rejoined as long as the process claims do not precipitate new rejections and are the same scope as the product claims.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 24-29, and 41 are withdrawn from consideration by the Examiner as they are drawn to non-elected inventions.

Specification

2a. It is noted that this application is a continuation of PCT Application No. PCT/Hu98/00086, filed on 09/18/97. A reference to the prior application must be inserted as the first sentence of the specification of this application if Applicant intends to rely on the filing date of the prior application under 35 U.S.C. 120. See 37 CFR 1.78(a).

It is suggested that below the title of the invention be inserted:

Cross Reference to Related Applications

"This Application is a continuation of PCT/Hu98/00086".

Appropriate correction is required.

2b. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
© Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(I) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

There are 9 figures in this Application, however, the section titled "Brief Description of the Figures" describing the figures is missing. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-23 and 30-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a water soluble composition comprising the compounds recited in claim 8, said compounds attached to human serum albumin in a non-covalent fashion, is non-enabling for "all" possible water -soluble compositions comprising the substances recited in claim 7, linked non-covalently to "all" possible animal plasma proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-7, recite "a water soluble product .....containing a therapeutically active compound having low aqueous solubility and a substantial binding affinity to plasma proteins ....", while, the specification discloses only compositions comprising paclitaxel, camptothecin, amphotericin, carbamazepine, cyclosporin A, or propofol attached to human serum albumin, (see page Examples II.1-II.35, on pages 16-25). The specification discloses, that the above mentioned compounds all have serum albumin binding affinities, and that the drugs retained their biological and therapeutic activities when linked to human serum albumin while becoming more soluble, see tables II A and II B, which compares the effects of paclitaxel in absolute alcohol and paclitaxel attached to HSA on MCF7 breast cancer cell proliferation. Instant specification also discloses in vivo pharmacokinetics tests comparing the drugs prepared in the conventional method and when the drugs were prepared following the method of the instant invention, (see page 29). Consequently, the instant specification is enabling for composition comprising a drug having low water solubility, attached to albumin, said composition retaining biological activity both in vitro and in vivo. Thus, the instant specification is only enabling

for water-soluble compositions comprising, drugs having low water solubility and having binding affinity for albumin, attached to albumin. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which of the disparate agents recited in claim 7 have binding affinity for human serum albumin, generate compositions comprising said agents attached to HSA, test if said compositions retained biological activity while becoming more soluble, is practically infinite and the guidance provided in the specification very little. Absent further guidance from the specification, it would require undue experimentation, to delineate if the all the agents recited in claim 7 have binding affinities for all the proteins recited in claim 6, (glycoproteins, interferons, or interelukins), conduct the necessary experiments to show that indeed these agents do bind to said proteins, test if the composition comprising drug-protein, retain biological activity and become water soluble. With respect to the proteins recited in claim 6, the instant specification is only enabling for a composition comprising drugs bound to immunoglobulin, the specification discloses compositions attached to immunoglobulin, (see example II.4 on page 17), and shows that said compositions are active and water soluble. However, the instant specification, does not disclose compositions comprising drugs attached to interferon, interleukins or glycoproteins.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23, 30-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 1 and 2, are vague and confusing: the claims recites "a water-soluble product or pharmaceutical formulations in solid or liquid form and *their organic solvent free true aqueous solutions*.....", it is unclear what is meant by "*their organic solvent free true aqueous solutions*", does this mean that the desired composition is totally water soluble and there is no organic solvent? Claim 1 also recites ".....substantial binding affinity to plasma protein (in the following "active substance"), in an interlinked state with a plasma protein fraction ....", this is totally confusing, firstly, "substantial' is a vague term, how substantial?, secondly, the phrase *(in the following "active substance")* is confusing. Claim 1 is very confusing, and Examiner had to interpret what is being claimed, (see paragraph 6a of this office action).

4b. Regarding claim 1, the phrase "optionally" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

4c. Regarding claims 2, 9-20, 23, 30, the phrase "preferably" renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

4d. Regarding claim 38, the phrase "characterized"renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

4e. Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim.

4f. Claim 21 whcih recites "a pharmacuetical formulation ...having a solid state or the form of an aqueous solution", is vague, it is unclear how can the pharmacuetical formulation have a solid state or the form of an aqueous solution. Clarification is required.

4g. The "and/or" alternative recited in claims 6, 23, 30-37, is confusing, for example, in claim 32-35, does the claimed composition contain the drug, and human serum albumin and recombinant human plasma albumin and γ globulin. Appropriate correction is required.

Claims 3, 4, are rejected as being vague and indefinite insofar as they depend on claim 1.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

102 rejs

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6a. Claims 1-11, 21-23, 30-31, 36, 38, 40-41 are rejected under 35 U.S.C. 102 (b), as being anticipated by Satoh et al (EP 0326618).

For this rejection, claim 1 of the instant application has been interpreted as reciting: a water-soluble pharmaceutical formulation in liquid or solid from, said formulation containing a therapeutically active compound (having low aqueous solubility, and having binding affinity to plasma proteins), bound to plasma protein.

Satoh et al teach a pharmaceutical composition comprising a drug having very low solubility in water, and having a protein binding property, said drug attached by hydrophobic bonding to

albumin, and is in a solid or liquid form, wherein said albumin is human derived albumin, wherein the solvent is removed by distillation, (page 3, lines 18-28 and page 28, lines 5-20 and claim 4), said pharmaceutical composition, also contains nontoxic pharmaceutically acceptable carriers, preservatives and stabilizers, (instant claims 1, 3, 4, 5, 7, 8, 9, 21-23, 31, 39-41). Satoh et al also disclose a method of treatment comprising administering said pharmaceutical composition as medicine, (bridge between page 7 and page 8). The pharmaceutical composition taught by Satoh et al comprises 1-200 part by weight of the and 100 parts by weight of the albumin, (page 3, lines 18-28), (instant claims 2, 10, 30). The Satoh et al reference teaches a pharmaceutical composition comprising the specific drugs recited in claims 8, 11, 30 and 36 (azathioprine, carbamazepine, clonazepam, cycosporing or amphotericin B) attached to albumin, (see pages 6 and 7). The Satoh et al reference clearly anticipated claims 1-11, 21-23, 30-31, 36, 38, 40-41, because it teaches a pharmaceutical composition with all the limitations recited in said claims.

6b. Claims 1-9 are rejected under 35 U.S.C. 102(b), as being anticipated by Mitsuharu, Inaba (JP 58-216126).

Mitsuharu teach a compost comprising water-insoluble drug and human serum albumin, said drug becoming soluble after it is dissolved in a solution comprising human serum albumin and water, (see abstract) and claims 1-9.

Claims 1-9 of instant application are drawn to a pharmaceutical composition comprising a water insoluble drug and albumin. Therefore Mitsuharo's reference anticipates the instant claims 1-9 in the absence of any evidence to the contrary.

6c. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

6d. Claims 1-10 are rejected under 35 U.S.C. 102 (e), as being anticipated by Desai et al (Us Patent 5,916,596).

Desai et al teach a pharmacologically active agent in combination with albumin, (see abstract). In a preferred embodiment Desai et al teach a pharmaceutical composition comprising taxol or paclictaxel and albumin, said composition having low toxicity, and said composition administered by intramuscular, or intravenous route of administration, (column 8, lines 5-15).

Claims 1-10 of the instant application are drawn to a water-soluble composition composing an active compound and plasma protein, said compost administered parenterally, (claim 10 limits this compost to paclitaxel).

Therefore Desaie's reference anticipates the instant claims 1-10 in the absence of any evidence to the contrary.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claims 1, 12-20, 32, 34-35, 37, 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Satoh et al (EP 0326618).

The teachings of Satoh et al is set forth above in paragraph 6a. However, Satoh et al do not disclose a pharmaceutical composition comprising the specific drugs recited in claims 12-20, 32-35 and 37, or a method of parenterally administrating said composition.

With respect to claims 1, 12-20, 32-35 and 37, which recite a formulation comprising human serum albumin containing specific drugs (campotothecinm gemafirozil, miconazole, propfol, tamoxifen, ritonavir, tacrolimus , tirilized, trioxsalen, pacilitaxel), it would have been obvious to one of ordinary skill in the art at the time of the invention, to formulate a composition comprising the recited drugs and human serum albumin, because Satoh et al demonstrated that any drug that has low solubility and has a binding affinity for albumin could be attached to albumin in a hydrophobic manner to generate a drug-albumin composition, said composition having less undesirable side effect, and results in improved absorption and light stability of the drug, (see page 28, lines 5-13). With respect to claims 39-41 which are drawn to parenteral administration of the composition of the instant invention, it would have been obvious to one of ordinary skill in the art to administer said pharmaceutical composition parenterally, because Satoh et al show that the composition comprising

drug and albumin, is orally active, therefore, it would be expected to be active if administered parenterally. One of ordinary skill in the art would have been motivated to generate a composition comprising the specific drugs recited in claims 12-20, 32-35 and 37 and human albumin, because attachment of drugs with low solubility to albumin, results in increased solubility, and therefore, increased therapeutic activities, and less undesirable side effects.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1646
March 11, 2000

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER